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NARRATIVE REVIEW

Current standard of care for septic shock

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Abstract

Sepsis is a syndrome of life-threatening organ dysfunction that results from dysregulated host response to infection, with septic shock defined as persistent hypotension despite fluid resuscitation, a serum lactate > 2 mmol/L and the need for a vasopressor infusion to maintain a mean arterial pressure of at least 65 mmHg. Approximately, 49 million cases of sepsis are recorded worldwide annually, with 11 million sepsis-related deaths, the majority occurring in patients with septic shock. A substantial proportion of survivors suffer from moderate to severe functional limitations including physical, cognitive and psychological disability, exacerbation of pre-existing chronic conditions and a high incidence of re-hospitalisation in the first 12 months after the initial diagnosis. Optimal management of patients with septic shock requires prompt and reliable recognition of patients with sepsis who require additional haemodynamic support. Initially, patients will need judicious intravenous fluids and consideration of the need for vasopressors such as norepinephrine. Administration of appropriate antibiotics and consideration for control of the source of infection are also required. In the optimisation phase, depending on patients' comorbidities and response to therapy, the balance of fluid therapy, vasopressors and potentially the addition of an inotropic agent will need to be adjusted, based on clinical findings and haemodynamic and biochemical parameters. For those patients who do not respond to initial therapy, more intensive monitoring may be required with consideration of adjunctive therapies such as corticosteroids, vasopressin, angiotensin II or other rescue therapies to achieve cardiovascular stability. Once stability has been achieved, clinicians need to consider strategies to ameliorate the potential long-term effects on survivors, while keeping in mind the perspective and experience of their patients.

Keywords: Sepsis, Septic shock, Resuscitation, Antibiotics, Antimicrobials, Critical care, Intensive care medicine

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Introduction

Sepsis is a syndrome of life-threatening organ dysfunction that results from dysregulated host response to infection [2]. Septic shock, identified in patients who, despite adequate fluid resuscitation, require a vasopressor infusion to maintain a mean arterial pressure of at least 65 mmHg and have a serum lactate > 2 mmol/L [2] is a condition with profound metabolic and circulatory disturbances and is associated with an increased risk of death and long-term morbidity. Approximately, 49 million cases of sepsis are recorded worldwide annually, with 11 million sepsis-related deaths [3]. In addition to mortality, more than 38 million survivors of sepsis are known to suffer from a range of biological abnormalities, cognitive and psychological impairments, adverse socioeconomic effects, exacerbation of pre-existing medical conditions and long-term adverse effects [4]. Sepsis has been recognised as a significant global health issue by the World Health Organization [5].

Optimal management of patients with septic shock requires prompt and reliable recognition of patients with sepsis who require additional haemodynamic support. In the initial phase, patients will need the judicious administration of intravenous fluid and consideration of the need of vasopressors such as norepinephrine. Administration of appropriate antibiotics and, where appropriate, control of the source of infection are also required. After this, in the optimisation phase, depending on patients' comorbidities and response to therapy, the balance of further fluid therapy and vasopressors will need to be adjusted, potentially with the addition of inotropic agents, based on clinical findings and haemodynamic and biochemical parameters [6]. When the initial therapy is insufficient to reverse the shock state, more intensive monitoring may be required with consideration of adjunctive therapies such as corticosteroids, vasopressin, angiotensin II or other rescue therapies to achieve cardiovascular stability. Once stability has been achieved, clinicians need to consider strategies to ameliorate the potential long-term effects on survivors. While other aspects of care such as those surrounding the indications and methods of providing ventilatory support and renal replacement therapy are important in the management of critically ill patients with septic shock, in-depth discussion of these is beyond the scope of this review. Recommendations specific to resource-limited settings are available to guide readers from these settings [7]. The aim of this manuscript is to provide an overview of the current best practice in the management of patients with septic shock, focusing on haemodynamic management (Fig. 1), so that clinicians can combine this information, with their clinical expertise and experience, as well as the perspective of patients (Box 1), to provide optimal care to their patients within their clinical setting.

Take home message

Current optimal management of patients with septic shock involves prompt recognition, judicious use of intravenous fluids and vasopressors, early administration of appropriate antibiotics, regular clinical reassessment and use of more advanced monitoring in those not responding to initial therapy to guide the addition of inotropic agents, adjunctive corticosteroids and potentially additional vasopressors. As the long-term consequences of septic shock can be significant, the impact of septic shock on patients and their families and loved ones should be borne in mind throughout the patients' journey.

Box 1: A patient's perspective

As a patient who has experienced and survived septic shock, the need for early recognition cannot be overstated. While early detection and the effective implementation of a sepsis pathway saved my life, primary health education may have gotten me to the emergency room sooner. When you are critically unwell, every moment counts. Many who have suffered sepsis look back on our experience and wish that the signs had been identified and acted on sooner. We want health professionals to be trained to recognise sepsis quickly, communicate clearly with us and our carers, and ensure that we become meaningful partners in our own healthcare. Throughout our hospital stay, we need to be kept informed. When we are too unwell to comprehend, our families and carers need to be part of the conversation. Being consulted about care decisions not only supports our dignity but can help prevent trauma. When clinicians use a trauma-informed approach to care provision, take care to explain procedures, and build relationships, they reduce feelings of fear and hopelessness, increase psychosocial support, feelings of autonomy, and patient/carer empowerment[1]. It is frightening to undergo invasive emergency procedures, to wake up in intensive care, to have no idea what happened or what comes next. It can be just as frightening to watch this happen to a loved one.

I feel incredibly lucky to have survived septic shock knowing that many people with septic shock do not survive. For those who are afflicted by septic shock, patients, their carers, and the bereaved, we need support to recover. Patients and carers should be educated about the potential long-term effects of sepsis, including physical, cognitive, and psychological issues. A clear picture of what recovery may involve, and a coordinated approach to physical rehabilitation,

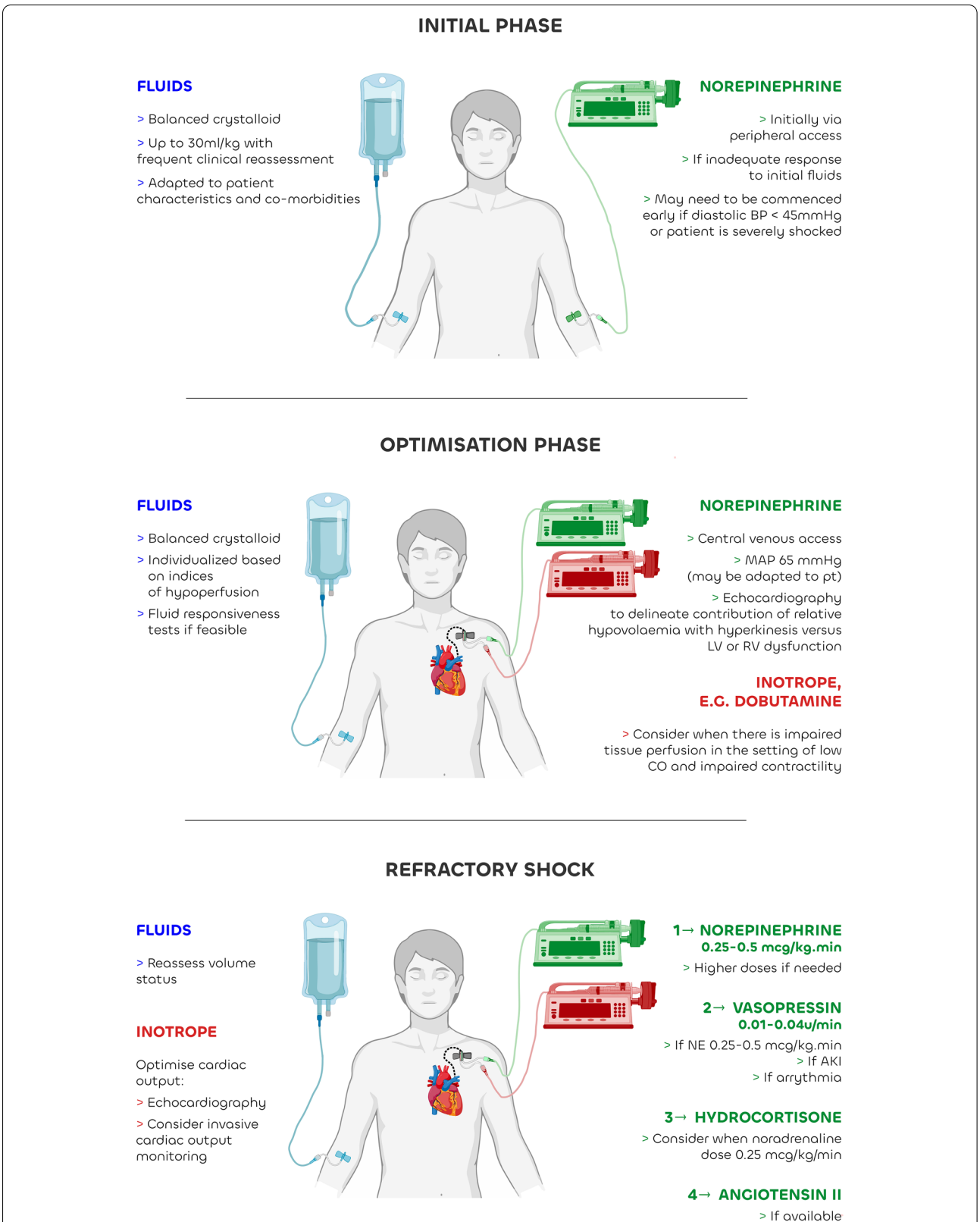
INITIAL PHASE
FLUIDS
> Balanced crystalloid
> Up to 30ml/kg with frequent clinical reassessment
> Adapted to patient characteristics and co-morbidities
NOREPINEPHRINE
> Initially via peripheral access
> If inadequate response to initial fluids
> May need to be commenced early if diastolic BP < 45mmHg or patient is severely shocked
OPTIMISATION PHASE
FLUIDS
> Balanced crystalloid
> Individualized based on indices of hypoperfusion
> Fluid responsiveness tests if feasible
NOREPINEPHRINE
> Central venous access
> MAP 65 mmHg (may be adapted to pt)
> Echocardiography to delineate contribution of relative hypovolaemia with hyperkinesis versus LV or RV dysfunction
INOTROPE, E.G. DOBUTAMINE
> Consider when there is impaired tissue perfusion in the setting of low CO and impaired contractility
REFRACTORY SHOCK
FLUIDS
> Reassess volume status
INOTROPE
Optimise cardiac output:
> Echocardiography
> Consider invasive cardiac output monitoring
1→ NOREPINEPHRINE
0.25-0.5 mcg/kg.min
> Higher doses if needed
2→ VASOPRESSIN
0.01-0.04u/min
> If NE 0.25-0.5 mcg/kg.min
> If AKI
> If arrythmia
3→ HYDROCORTISONE
> Consider when noradrenaline dose 0.25 mcg/kg/min
4→ ANGIOTENSIN II
> If available

Fig. 1 Haemodynamic management of patients with septic shock. *BP* blood pressure, *MAP* mean arterial pressure, *CO* cardiac output, *AKI* acute kidney injury

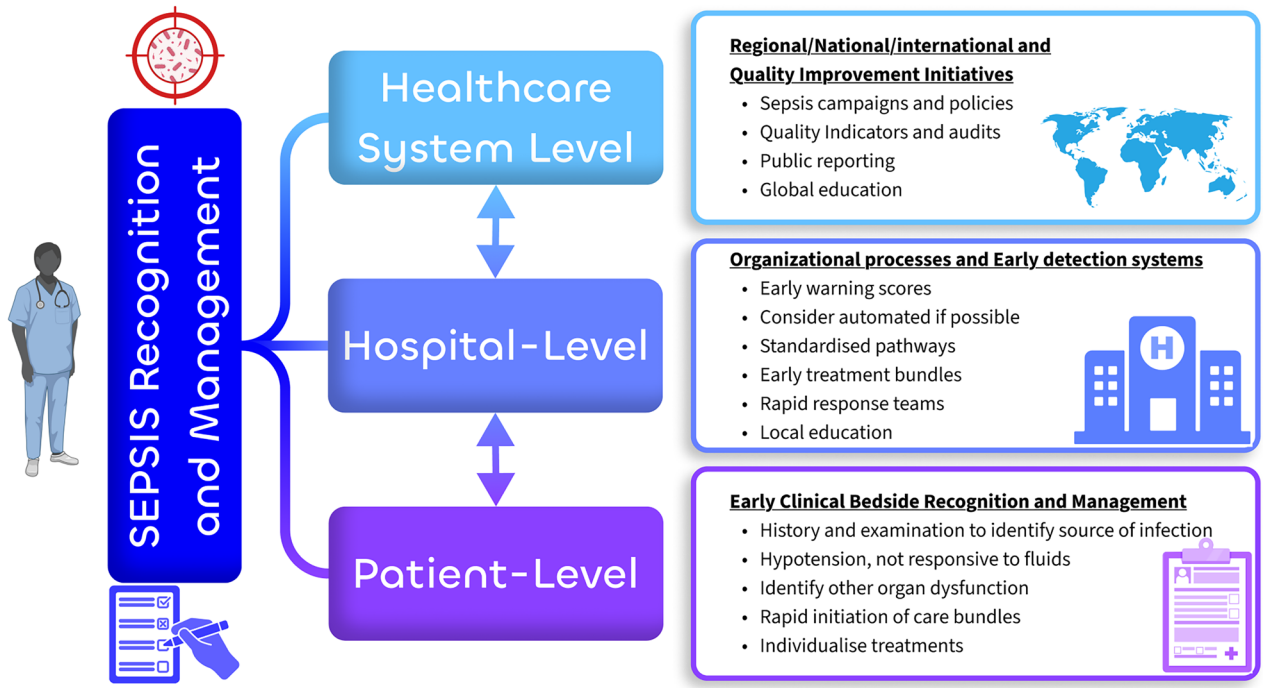

Fig. 2 Sepsis recognition and management

mental health support, and social/workforce reintegration should be considered our rights. Coordinated follow-up care is essential, especially when navigating complex needs across multiple services. Those of us who have experienced sepsis need to be empowered to reclaim our lives—we want more than survival.

Recognition

Early recognition of sepsis and septic shock remains critical to improving outcomes, yet sepsis is frequently underdiagnosed or recognised too late in many hospital settings. Current diagnostic approaches rely on clinical judgement, vital signs and laboratory results (e.g. lactate, inflammatory biomarkers). The early identification of patients with sepsis, based on individual clinical features, remains difficult due to the often nonspecific and heterogeneous clinical presentations. Septic shock may be readily recognisable in those with an elevated lactate and a requirement for vasopressors, but may require a higher degree of clinical suspicion to detect in patients with persistent signs of hypoperfusion that are not responsive to initial fluid therapy and should prompt an escalation of care [7]. It is also important not to overdiagnose sepsis, as this may lead to delays in treating the real cause of shock and administration of non-indicated antibiotics, promoting antibiotic resistance. Sepsis recognition is thus a delicate balance (Fig. 2).

The variability in clinician expertise, delays in obtaining results and/or limited availability of biomarkers imply that a systematic approach to screening at an institutional level may be required to improve the recognition of sepsis. This includes the use of scoring systems such as Systemic Inflammatory Response System criteria, Sepsis related Organ dysfunction Score (SOFA), or quick SOFA (qSOFA), and early warning tools such as National Early Warning Score (NEWS) and Targeted Real-time Early Warning System. [8] A recent meta-analysis identified NEWS as having the best combination of sensitivity and specificity for identifying patients at risk of sepsis and adverse outcomes, particularly in emergency departments [9]. The qSOFA score has been shown to have insufficient sensitivity to be used as a screening tool [10]. However, while scoring systems may improve the detection of patients at risk of sepsis, none are sufficient to ensure the early recognition of patients with sepsis across healthcare systems.

Addressing this requires systematic multifaceted strategies. Standardised protocols, evidence-based guidelines (e.g. Surviving Sepsis Campaign), and targeted educational programmes have demonstrated improved early detection. Local initiatives such as sepsis codes [11] and audit-feedback systems, along with international efforts

like the Global Sepsis Alliance, promote structured approaches [12]. Sepsis Code programmes rest on four pillars: early detection, multidisciplinary collaboration, continuous education, and rapid response. Timely activation of sepsis codes correlates with improved outcomes [12].

Technological innovations present new opportunities to improve the recognition of patients with septic shock. Automated electronic detection systems, using real-time electronic health record data, can generate sepsis alerts, enabling earlier interventions [13]. Machine learning models trained on large datasets, wearable biosensors and novel biomarkers, do not represent the current standard of care [14].

Haemodynamic resuscitation

Maintenance of adequate blood pressure and perfusion in septic shock is of critical importance to prevent organ system failure. Currently, a mean arterial pressure of at least 65 mmHg is the standard established by the Surviving Sepsis Campaign as an initial goal, though a more individualised target, taking into account age, pre-existing blood pressure and comorbidities may be considered [15]. Pooled data from meta-analyses have not provided a clear universal blood pressure goal [16], with a recent reanalysis of the SEPSISPAM trial [17] failing to demonstrate heterogeneity of treatment effect in response to allocation to higher or lower blood pressure targets [18]. The restoration of adequate blood pressure and perfusion requires administration of intravenous fluid for resuscitation, as well as the administration of vasopressors, consideration of the need for inotropic agents and possibly corticosteroids, with the balance of these therapies guided by patients' response to therapy as indicated by clinical examination, biochemical testing and via monitoring techniques to achieve the individual therapeutic goals in each particular circumstance.

Fluid therapy: type of fluid and volume of fluid

Fluid resuscitation is a cornerstone in the management of sepsis and septic shock. Crystalloids are recommended as the first-line fluid for initial resuscitation in patients with sepsis and septic shock due to their wide availability and low cost, as well as view of the lack of clear benefit associated with the use of colloids [15].

The choice of crystalloid type has been explored in several recent randomised clinical trials. Current evidence favours balanced crystalloids over isotonic saline. An individual patient data meta-analysis including 34,685 patients found a 97.5% probability that balanced crystalloids reduce the risk of new renal replacement therapy initiation compared with saline [19]. The impact on mortality was less definitive, with a posterior probability of mortality reduction of 89.3% associated with balanced solutions. Both the Surviving Sepsis Campaign [15] and European Society of Intensive Care Medicine (ESICM) [20] guidelines recommend balanced crystalloids over isotonic saline for volume resuscitation in adult critically ill patients with sepsis. Clinicians may need to consider particular circumstances such as when patients present with alkalosis or hypochloraemia, as well as the relative costs in their location when making choices regarding the particular crystalloid fluid.

With regard to colloids, hydroxyethyl starches should be avoided, as their use has been linked to increased mortality and a higher need for renal replacement therapy [21]. The role of albumin remains controversial. Although albumin offers theoretical advantages, such as greater plasma-expanding capacity and maintenance of oncotic pressure, these benefits may be attenuated by the increased capillary permeability observed in sepsis. In the absence of clear harm and based on improvements in certain physiological end points [22], the Surviving Sepsis Campaign suggests considering albumin in patients who have received large volumes of crystalloids [15]. The recent ESICM fluid management guidelines recommend the use of crystalloids alone [20], while acknowledging that in certain subgroups, such as patients with cirrhosis [23], hypoalbuminaemia or those requiring substantial volumes of crystalloids, clinicians may consider the use of albumin, while awaiting further evidence. Should clinical benefit be confirmed in these populations, cost-effectiveness analyses will be essential to inform future practice, particularly in resource-limited settings, where high cost and limited availability present additional barriers. The optimal concentration of albumin (e.g. 4% vs. 20%) also remains under debate.

The optimal amount of fluid to be administered remains controversial. The recent ESICM guidelines [24] recommend administering up to 30 mL/kg of intravenous crystalloids during the initial phase (when haemodynamic monitoring is not yet available), with adjustments based on clinical context and frequent reassessments. Observational data and recent trials report typical volumes between 20 and 35 mL/kg, but with wide variability between patients, and no study has specifically tested a given volume. Guidelines acknowledge that clinicians may choose to administer different volumes based on clinical judgement, individual patient characteristics, and context, such as the origin of sepsis, comorbidities or the presence or absence of fluid losses. Clinicians should also assess patients clinically and consider evaluating fluid responsiveness (if feasible) before administering additional crystalloids during the initial resuscitation phase,

recognising that some may require more or less than 30 mL/kg. This may be particularly pertinent in clinical settings with limited access to advanced haemodynamic monitoring and invasive support [25, 26],

There are data that demonstrate an association between excessive fluid accumulation and adverse outcomes [27], particularly among patients with comorbidities such as heart failure or kidney disease and in low-resource settings. In low-income countries, protocolised high-volume strategies have even been associated with increased mortality [28]. Conversely, in high-income settings, recent trials found no significant difference in outcomes between restrictive and liberal fluid strategies after initial resuscitation [29, 30], noting that the participants allocated to the liberal fluid arms of these trials received less fluid volume than had been considered standard in the recent past [31]. Current guidelines do not recommend for or against systematic restrictive or liberal fluid administration during the optimisation phase of sepsis, but instead promote an individualised approach over a non-individualised one when some form of haemodynamic monitoring is available [24]. Individualised fluid administration may be guided by several key strategies, including systematic assessment of fluid responsiveness [32], the use of fluid challenges, identification of basic haemodynamic phenotypes, and timely selection of appropriate resuscitation end points to minimise the risk of fluid overload.

Vasopressors

After commencement of fluid resuscitation, vasopressors may also be required to achieve an adequate haemodynamic status. However, there remains uncertainty regarding the optimal triggers to commence vasopressors. Meta-analyses examining early and delayed vasopressor initiation after fluid resuscitation provided conflicting results [33, 34]. In select cases, such as patients with low diastolic arterial pressure, signifying loss of vasomotor tone, along with the absence of bradycardia, more immediate vasopressor initiation might be prompted [35].

Norepinephrine is the recommended and accepted first-line agent to achieve the blood pressure goal [15]. Norepinephrine may be commenced via peripheral venous access, as this is generally safe in the short term with careful monitoring of the insertion site and allows for restoration of blood pressure while awaiting central venous access [15]. Variation in the formulations of norepinephrine makes comparisons between studies difficult and a statement supported by the Society for Critical Care Medicine and ESICM suggests the uniform adoption of norepinephrine base as a universal dispensing and reporting strategy [36]. This will allow for standardisation of clinical practices, research, quality and prognostication.

High-dose norepinephrine is used alone or in combination with other non-catecholamines or catecholamines for escalation of care. Consideration for escalation would usually occur when a norepinephrine (base) dose of 0.25–0.5 μg/kg/min is required to achieve the desired target blood pressure. Vasopressin is usually initiated as a second-line agent [37]. While data from randomised trials in patients with less severe septic shock do not convincingly demonstrate a mortality benefit, there was a suggestion of improved renal outcomes with the addition of vasopressin [38, 39]. Timing of initiation of vasopressin remains a matter of debate, where both timing from the onset of shock and timing as regard the dose of norepinephrine are taken as considerations. Reinforcement learning derived algorithms point to the survival benefit of early vasopressin use relative to shock onset (median [IQR], 4 [1–8] vs 5 [1–14] h), and at lower norepinephrine doses (median [IQR], 0.20 [0.08–0.45] vs 0.37 [0.17–0.69] μg/kg/min) compared to clinicians' actions [40]. An emulated target trial with over 3000 patients with septic shock also demonstrated the benefit of earlier introduction of this agent at < 0.25 mcg/kg/min of norepinephrine [41]. While attractive, these results are in opposition to the VANISH trial that initiated vasopressin within 6h of use of norepinephrine at a mean dose < 0.2 mcg/kg/min. Cost and scarcity may limit the use of vasopressin in some settings, and further clinical trial evidence is required to establish the role of vasopressin. Norepinephrine doses exceeding 0.5 μg/kg/min have been associated with poorer outcomes, including increased in-hospital mortality among septic shock patients, even though causality and the relationship with a single dose threshold are yet to be established [42]. Similarly, a dose, duration, threshold of single or multiple vasopressors and/or biomarkers that would allow septic shock to be termed refractory are yet to be clearly determined.

Approved in late 2017, angiotensin II is the newest vasopressor that is being used in clinical practice in the USA and the European Union [43], although it may not be available in all regions and settings. Some patients in septic shock suffer from major dysfunction of the renin–angiotensin–aldosterone system, and the strongest clinical benefit of angiotensin II has been seen in this setting [44]. It should be noted that while angiotensin II has been shown to increase blood pressure, its effect on patient centred outcomes remains unclear. If vasoplegic shock is not responsive to the above combination of vasopressors, clinicians sometimes consider adjuncts such as methylene blue and hydroxocobalamin [45], but the impact in

adequately powered clinical trials has not been tested yet. Additionally, this clinical scenario should also prompt consideration of the use of more advanced haemodynamic monitoring, the need for inotropic agents as well as adjunctive corticosteroids.

Inotropes

Current international guidelines suggest adding dobutamine to norepinephrine or using epinephrine alone in patients with septic shock and persistent hypoperfusion despite adequate fluid resuscitation and arterial pressure restoration, particularly in the presence of cardiac dysfunction [15]. Clinically, this is often indicated by persistent mottling, prolonged capillary refill time or elevated lactate and the absence of preload responsiveness assessed by dynamic tests. Cardiac dysfunction should be confirmed by echocardiography or invasive monitoring of cardiac output and may be inferred from signs of impaired oxygen delivery, such as low central venous oxygen saturation ($ScvO_2$) or an increased veno-arterial gradient of partial pressure of carbon dioxide (PCO_2 gap), which suggests inadequate cardiac output [46]. Sepsis-induced myocardial dysfunction is a frequent, condition marked by acute left and/or right ventricular systolic and/or diastolic dysfunction unrelated to coronary disease [47]. Dobutamine remains the most used inotrope, but its effect is variable in patients with septic shock due to β_1-receptor downregulation, and it may be associated with tachyarrhythmias and vasodilation [48], with the potential to precipitate adrenergic cardiomyopathy [49]. In the initial stages, norepinephrine alone may improve cardiac performance [50], but this effect is often insufficient in patients with overt cardiac dysfunction. Levosimendan, a calcium sensitiser, offers theoretical benefits in the setting of β_1-receptor downregulation [51], but failed to improve outcomes in a large clinical trial and a post hoc analysis even among patients with myocardial injury [52, 53]. Importantly, these studies did not target patients with confirmed low cardiac output and DO_2/VO_2 mismatch. Milrinone, a phosphodiesterase-3 inhibitor, bypasses the adrenergic pathway offering theoretical advantages, but has not been studied in clinical trials in patients with septic shock. Both levosimendan and milrinone are associated with vasodilation and have prolonged half-lives; the use of these agents requires careful consideration and close monitoring. Epinephrine remains an alternative, but is associated with lactic acidosis and potential splanchnic hypoperfusion, and may be associated with increased mortality [54].

Corticosteroids

Corticosteroids have been used since the 1970s in patients with septic shock and have been consistently shown to reverse shock. The mechanisms underlying an improvement in shock state include immune modulation, enhanced catecholamine release and improved pressor responsiveness [55]. However, the role of corticosteroids in improving mortality in septic shock remains unclear. Trials using intravenous hydrocortisone alone at a dose of 200mg/day have not demonstrated a reduction in mortality [56], but a combination of fludrocortisone plus hydrocortisone was shown to reduce mortality as compared to placebo [57]. Of note, patients included in the trial administering hydrocortisone (200 mg/day ivi plus fludrocortisone 50 μg/day enterally) were also more severely ill at baseline with much higher doses of vasopressor agents at baseline and associated high mortality in the placebo group. No definitive evidence exists to guide the timing of commencement of corticosteroids; guidelines recommend considering commencement when noradrenaline infusion rates reach 0.25 μg/kg/min [15].

It should be noted that the potential benefits from the use of corticosteroids in patients with septic shock may not be apparent in all patient subgroups. A post hoc analysis revealed that this beneficial effect in the APROCCHSS trial was restricted to those with septic shock secondary to community-acquired pneumonia, but not in non-pulmonary sepsis raising the possibility of a heterogeneity of treatment effect [58]. Evidence for heterogeneity of treatment effect of corticosteroids is also demonstrated in secondary analyses of clinical trials which suggest that endotypes based on transcriptomic, endocrine, metabolomic or cytokine-based signatures may benefit from or be harmed by steroids, not evident from the main clinical trial results [52]. The role of fludrocortisone in septic shock and identifying endotypes that predict corticosteroid responsiveness and the role of corticosteroids in resource-constrained settings remain areas of ongoing investigation.

Goals of resuscitation

The ultimate goal of septic shock resuscitation is a prompt reversal of tissue hypoperfusion. Resuscitative interventions are guided by haemodynamic and perfusion monitoring, and adapted to the specific phase of septic shock [59, 60]. Early on, simple and universally available monitoring signals such as vital signs, capillary refill time, as well as changes in lactate levels, may allow clinicians to tailor resuscitation according to the predominant macrohaemodynamic pattern [61]. Personalised haemodynamic resuscitation targeting CRT and using various tests including fluid responsiveness tests and echocardiography was shown to improve the composite end point associating mortality, duration of vital support and length of hospital stay at 28 days [6].

From a perfusion perspective, several variables have been used to diagnose hypoperfusion, monitor response to haemodynamic interventions or as resuscitation targets [61]. The three clinical windows for assessing perfusion are mental state, skin perfusion and urine output. More recent research has focused on capillary refill time as a monitor, but also a novel resuscitation target supported by a number of observational studies, physiological context and a recent randomised clinical trial [62, 63]. Capillary refill time is a cheap and universally available monitor and as such has been suggested by the current guidelines of the Surviving Sepsis Campaign [15]. Importantly, capillary refill time has to be assessed in a trained and standardised way to improve inter-rater reliability [63].

Hyperlactataemia has traditionally been seen as a signal of anaerobic metabolism. However, it is a complex signal, reflecting not only tissue hypoxia in the context of hypoperfusion, but also aerobic production in the context of adrenergic stimulation, or a decreased lactate clearance. It has been recently challenged as a resuscitation end point, as targeting changes in lactate levels has not been shown to be an effective strategy to guide resuscitation [63, 64]. Its slow kinetics of recovery make lactate an inadequate variable to fine-tune rapid haemodynamic interventions [61], although its recovery trend may add relevant prognostic information.

In patients with a central venous catheter in place, ($ScvO_2$) and venous-arterial pCO_2 gradient (pCO_2 gap) may aid in interpreting macrohaemodynamic status and deciding on further interventions in complex septic shock patients with persistent hypoperfusion [1, 16, 59]. A low $ScvO_2$ and/or a high pCO_2 gap may signal an inadequate cardiac output, thus promoting further macrohaemodynamic optimisation. Conversely, a high $ScvO_2$ in a deteriorating patient may suggest a severe microcirculatory dysfunction with macro-to-microcirculatory uncoupling. Targeting $ScvO_2$ values of 70% has been shown ineffective [65]. With no specific marker of adequacy of resuscitation, clinicians will need to use all information available in their clinical setting to adjust therapies to ensure an optimal haemodynamic state.

Haemodynamic monitoring

Haemodynamic monitoring is used to ensure that the goals of therapy in critically ill patients with septic shock are being met. Invasive arterial blood pressure monitoring is preferred as an intermittent oscillometric method, but it is not reliable during haemodynamic instability [3, 66] and does not provide continuous measurements or have the ability for rapid blood sampling. In addition, the monitoring of invasive arterial pressure allows further adjustments of therapy guided by simple haemodynamic variables such as pulse pressure and diastolic arterial pressure [67]. A recent trial showed that delayed use of an arterial catheter was non-inferior to early arterial catheterisation, noting that many patients were excluded from the trial due to the presence of severe shock or impossibility to measure blood pressure non-invasively [68]. Hypotension with a low pulse pressure suggests a low stroke volume that in this setting is probably related to a decreased preload triggering further fluid resuscitation in confirmed fluid-responsive patients. Conversely, hypotension with normal pulse pressure and low diastolic arterial pressure is a hallmark of severe vasoplegia that may be better managed by commencing or making adjustments of norepinephrine [67].

Cardiac output should be monitored in patients who do not respond to initial therapy to assess the type of shock, evaluate haemodynamic status and determine therapeutic strategies, as a mixed picture of vasoplegic–cardiogenic shock may complicate the assessment and determination of appropriate therapeutic strategies. In cases with mixed vasoplegic and cardiogenic shock, measured cardiac output (as well as the SvO_2 and PCO_2 gap) may be normal, but may still be inadequate to meet the pathophysiological demands required in a state of septic shock. Apart from clinical assessment, echocardiography is the first-line tool for evaluating the type of shock to obtain rapid information on cardiac function and to exclude major pathologies that require immediate treatment [69, 70]. Pulmonary artery catheterisation using a Swan-Ganz catheter[r] or pulse contour analysis with transpulmonary thermodilution technique is a reasonable approach for the estimation of cardiac output, and the choice of which method to use will be guided by availability and local experience, so that known adverse events may be minimised. Transpulmonary thermodilution may be preferred because it measures extravascular lung water (EVLW), providing a useful quantification of alveolar interstitial oedema [71]. Further, measurement of the pulmonary vascular permeability index may provide valuable information regarding the aetiology of EVLW, with pulmonary vascular permeability index > 3 indicating capillary leak [72]. In patients with right ventricular failure or pulmonary hypertension, the pulmonary artery catheter may be preferred because pulmonary artery pressures are directly measured.

Cardiac output measurement is also required for measuring the response to a fluid challenge (200–500 mL bolus over 5–10 min), and pulse contour analysis can readily fulfil this role. Dynamic variables are preferred over static markers of preload for predicting fluid responsiveness; however, pulse pressure variation and stroke volume variation alone are not reliable in many ICU patients [73]. For example, arrhythmias, low tidal volume

ventilation, preserved spontaneous breaths and intra-abdominal hypertension invalidate pulse pressure variation and stroke volume variation as predictors of fluid responsiveness. Functional haemodynamic tests such as passive leg raising, tidal volume challenge, end-expiratory occlusion, Trendelenburg and positive end-expiratory pressure tests [74], evaluated by changes in cardiac output or stroke volume provide useful assessments of fluid responsiveness, but require precise and continuous monitoring techniques such as pulse contour analysis.

Point of care ultrasound can be used for repeated echocardiography to complete the haemodynamic assessment, even when cardiac output is monitored, as well as to assess the response to fluid, to determine when sufficient volume has been administered and to assess the response to vasopressor and inotropic therapy [75].

Antibiotics and source control

With the management of sepsis and septic shock often focused on supporting organ systems, the mainstay of the treatment of infection is antibiotic therapy and source control.

Infections that incite sepsis are caused by infective agents which vary according to the primary source of infection and also vary according to geographic region. Initial antimicrobial therapy will need to be targeted according to the most likely pathogens based on the patients' clinical presentation, comorbidities and local and regional patterns of infection. For example, respiratory infections in patients presenting to the emergency department are commonly caused by Gram-positive organisms [76], whereas urinary tract and abdominal infections are usually secondary to gram-negative organisms. Hospital-acquired infections are usually caused by gram-negative organisms which are more often resistant to antibiotics [77]. Empirical therapy should be aimed at the pathogens most likely to cause the infection [78].

It is important that each Intensive Care Unit has up-to-date susceptibility data from pathogens causing infections to guide this empirical therapy. Such flora vary from country to country and may differ from areas within a country, even across hospitals [79]. It is important not to delay the start of antibiotics when needed in sepsis and septic shock, as delays in the initiation of antibiotics are associated with higher mortality [80, 81]. New insights have shown that adequate dosing, including consideration of the appropriate loading dose, and optimised administration of antibiotics can further improve the efficacy of the treatment [82]. Augmented renal clearance is a common finding in critically ill patients [83] and leads to underdosing; adapting the dose accordingly, complemented with therapeutic drug monitoring if available, is increasingly advocated for many antimicrobials in the critically ill [84]. For beta-lactam antibiotics, prolonged infusion has been associated with lower mortality rates [85].

At all times there should be cogent thought provided to the balance between reasoned empiric use and the quick discontinuation or de-escalation when possible [78]. The downside of antibiotic use—such as change in bowel flora, overgrowth of resistant organisms on skin and in bowel—creates an environment that a "standard" course of antibiotics should be limited to eradicating the infected cause, but little longer. A 2-week course should be curtailed to 5–7 days [86], in patients without immunosuppression who are responding well to therapy, in the absence of multidrug-resistant organisms, unless source control is impossible or incomplete, in deep-seated infections or in special circumstances such as staphylococcal infections.

Whilst it is prudent to use the correct antibiotics for each infection, removing as much of the infected load of any contaminated area should be a priority. This may mean cleaning the wound, debriding areas of tissue or accessing areas to drain debris and as much of the bacterial (or fungal) load as practical. Such management strategies—source control—have become the mainstay of initial management of many infections. Source control refers to all measures undertaken to eliminate or control any ongoing infected area with the aim of not only decreasing the infected load, but also restoring as much of the premorbid anatomy and function as possible (Fig. 3) [87].

Initially source control was limited to the removal of infected foreign bodies such as central venous catheters or other indwelling devices or drainage of accessible collections such as intra-abdominal infections by means of a laparotomy. With newer, sophisticated imaging and new minimally invasive strategies, many collections of pus, debris and infected material can be relatively easily drained without the need for open surgeries. Computerised tomography has been the primary technique to guide source control procedures, but ultrasound access is increasingly available and this could make source control more accessible for low-resource settings. Source control therefore should be considered in all cases of sepsis or septic shock and, whilst not always practicable (e.g. an infected joint or heart valve, pneumonia without abscesses), should be considered as an early part of all treatment strategies [88]. Such management strategies have been shown to decrease mortality in many forms of relevant community-acquired sepsis [89].

Long-term recovery

Sepsis and septic shock can lead to significant long-term sequelae called post-sepsis syndrome (PSS)[90] that

Table 1 Impact of post-sepsis syndrome

Neurological impact	Neuroinflammation, blood–brain barrier dysfunction and the accumulation of neurotoxic proteins can lead to acute and chronic cognitive impairment. Survivors often experience difficulties with memory, concentration and executive functions
Cardiovascular impact	Myocardial dysfunction involves inflammatory mediators such as TNF-α and IL-6, contributing to heart failure and other cardiovascular complications
Renal impact	Sepsis-associated acute kidney injury arises from hypoperfusion and inflammation, increasing the risk of progression to chronic kidney disease
Psychological impact	Anxiety, depression and post-traumatic stress disorder are prevalent among survivors
Physical impact	Disability due to limb amputations, muscle weakness, fatigue, difficulty swallowing and difficulty sleeping
Other considerations	Social, family and caregiver impact including complicated grief, mental health concerns and bereavement support

may share similar outcomes with other post-critical illness constructs such as post-intensive care syndrome. PSS encompasses a range of long-term physical, psychological, and cognitive impairments that persist after the acute phase of sepsis has resolved [91]. The prognosis for patients after sepsis varies with approximately one-third of patients dying in the year following sepsis, one-sixth experiencing severe persistent physical or cognitive difficulties, and only half of the survivors having a complete or near-complete recovery [91, 92].

PSS is characterised by prolonged immune dysregulation, chronic inflammation and metabolic and endothelial dysfunction. These factors predispose survivors to recurrent infections, cardiovascular disease and neurocognitive decline. Mitochondrial dysfunction and epigenetic modifications play central roles in prolonged immunosuppression, impairing both adaptive and innate immune responses. Sepsis-induced organ dysfunction impacts multiple systems, including the brain, heart and kidneys (Table 1) [93].

Best practices for recovery and follow-up

Effective management and prevention of PSS sequelae requires a comprehensive approach that observes the care continuum approach to optimise best practice. This includes early interventions which could be guided by the A-F bundle [94], early rehabilitation which may improve cognition [95], planned and tailored rehabilitation and follow-up.

While the literature is inconsistent for longer-term follow-up of critically ill sepsis patients, it is generally considered that follow-up via an ICU follow-up clinic, with specialty consultants or other rehabilitation services is important [96]. Follow-up, whether it is in person or virtual, provides an opportunity for evaluating post-sepsis syndrome, medication reconciliation, setting up rehabilitation appointments, referring patients to support programmes and identifying areas of concern that may lead to further decline in quality of life. Some suggested areas for review after the acute care admission include the following:

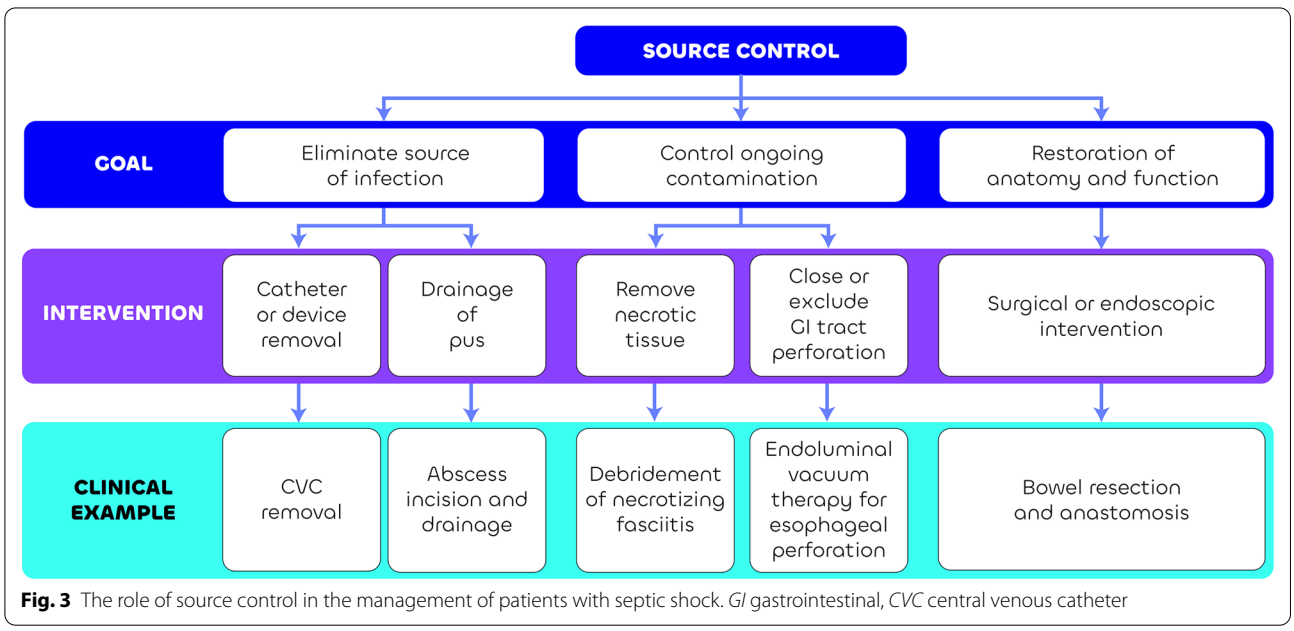

Fig. 3 The role of source control in the management of patients with septic shock. *GI* gastrointestinal, *CVC* central venous catheter

Medications: It is crucial to resume the right medications after hospitalisation, as dosages may need adjustment due to physiological changes such as weight loss or reduced kidney function. In addition, review of medications that have been started during the hospital admission and continued is important.

Risk evaluation and reduction: It is recommended that patients be screened for treatable conditions that commonly result in repeat hospitalisation, such as repeat infections, heart failure and renal failure.

Rehabilitation: New muscle loss and weakness are common among sepsis survivors. Physical therapy, occupational therapy or speech therapy may be necessary. Gradually increasing activity levels each day is important for rebuilding strength.

Support programmes: There is a growing network of support groups for patients and their family who have survived critical illness. These programmes may be useful for sepsis survivors too, as they can provide essential emotional support and practical advice for managing long-term symptoms and physical sequelae.

Summary

Optimal management of patients with septic shock requires prompt and reliable recognition of patients with sepsis who require additional haemodynamic support. The initial phase of haemodynamic management involves the judicious administration of intravenous fluid and consideration for vasopressors such as norepinephrine. Administration of appropriate antibiotics and where appropriate control of the source of infection are required. In the optimisation phase, depending on patients' comorbidities and response to therapy, clinicians need to consider further fluid therapy, adjustment of vasopressors and potentially the addition of inotropic agents based on clinical findings and haemodynamic and biochemical parameters. For those patients who are not responding to initial therapy, more intensive monitoring can guide considerations of the addition of adjunctive therapies such as corticosteroids, vasopressin and angiotensin to achieve cardiovascular stability.

Once stability has been achieved, clinicians need to consider strategies to ameliorate the potential long-term effects on survivors, while keeping in mind the perspective and experience of their patients.

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Declarations

Conflicts of interest
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